

BEDSIDE MEDICINE FOR BEDSIDE DOCTORS

An Open Forum for brief discussions of the workaday problems of the bedside doctor. Suggestions of subjects for discussions invited.

ENDOCRINE PREPARATIONS AND THEIR CLINICAL USEFULNESS

II*

LIVER EXTRACT AND SECRETIN

ARTHUR L. BLOOMFIELD, M. D. (Stanford University Hospital, San Francisco).—Liver as a therapeutic agent displays its most outstanding action in pernicious (Addisonian) anemia. Patients who eat large quantities of mammalian liver (calf, beef, hog), as first shown by Minot and Murphy, are relieved of the general symptoms of the disease and their blood counts rise to approximately normal levels. However, the disorder is not really cured; it is only kept under control; and even though the patient feels perfectly well, morphological changes of the red blood cells are still detectable, the achylia gastrica persists, and the central nervous system changes remain or may even progress. Experience in the past ten years indicates none the less that if people with pernicious anemia take liver faithfully they may live indefinitely at a reasonably high level of health. The term "pernicious anemia" has become a misnomer.

The beneficial effect of liver feeding is not yet clearly understood. In healthy people the "anti-anemic" substance seems to be elaborated in the stomach by interaction of normal gastric juice with certain (protein) food constituents, whence it is absorbed for storage in the liver. Evidence at present available indicates that this effective substance is either not formed or is not absorbed in the pernicious anemia patient, and it has in fact been shown to be absent from the livers of people dying of the disease. In the livers of pernicious anemia patients who died of extraneous causes *after liver therapy*, on the contrary, the effective substance has been demonstrated.

The principal objection to whole liver feeding is that patients tire of eating large quantities. Hence the effort to extract a potent liver fraction which can be taken in small bulk. These efforts have been successful, as every physician knows. We cannot go into the details of preparation here; suffice it to say that the so-called *fraction G* (of which approximately four grams represent the anti-anemic potency of 100 grams of fresh liver), is a *highly specific* product which is useful *only in pernicious anemia* and allied conditions, and *not in anemic states in general*. Fraction G, the pernicious anemia fraction, is now marketed by many pharmaceutical houses. It comes as a powder, which can be dissolved in warm water and taken as one would a "beef tea"; or it may be

obtained in capsules. There are also liquid preparations. The doses vary; those of individual preparations are stated on the container by the manufacturer. In general, *large* doses (the extract of about 200 to 400 grams of fresh liver) must be given daily to produce a satisfactory remission; when this is achieved, a smaller maintenance dose sufficient to hold the blood count at a normal level must be worked out for the individual patient. If the dosage is adequate, the hemoglobin level after a latent period of a few days should rise ten or more per cent weekly.

For desperately ill patients, for those who seem to have difficulty in absorbing the effective substance per os, or for those who object to the taste, preparations which can be given intramuscularly are available. The advantage of these highly concentrated extracts is that they act somewhat more rapidly and certainly than the mouth preparations, and when remission has been accomplished a single injection of a few cubic centimeters, at intervals of a week to a month or more, may suffice for maintenance. The disadvantage is that of any hypodermic technique, together with the possibility of local soreness at the site of injection, and an occasional constitutional reaction. In practice we advise that every physician familiarize himself with one good intramuscular preparation, and with one to be taken by mouth rather than to vaguely prescribe a variety with none of which he is expert.

Fraction G has also been found to exercise a specific beneficial effect in sprue, a disease which is, of course, closely allied to pernicious anemia. The diarrhea abates, the blood count rises and constitutional symptoms disappear. The procedure is the same as with typical Addisonian anemia.

Aside from sprue and pernicious anemia, Fraction G has been reported to relieve the anemia associated with *Diphyllobothrium* (fish tapeworm) infestation, and occasionally to be helpful in ill-defined states of diarrhea associated with gastric anacidity.

Liver feeding has a definite but less dramatic blood building effect in certain types of "secondary" anemia. Whipple showed that dogs, maintained in a state of chronic blood depletion, regenerated hemoglobin much more rapidly if liver was added to the diet. So, too, in man, among the secondary anemias the best results are obtained in those due to chronic blood loss. Liver has been used for anemia due to cancer, Bright's disease, and various intoxications or infections, but with variable or slight effect.

* Part I of this symposium was printed in March issue of CALIFORNIA AND WESTERN MEDICINE, page 181.

A so-called secondary anemia liver extract is available. This is to be clearly distinguished from the pernicious anemia extract (Fraction G) discussed above. It is derived from an entirely different liver residue and *the two extracts cannot be used interchangeably*. The dosage of secondary anemia fraction is not accurately standardized; one usually gives two or more teaspoonfuls three times a day dissolved in hot water and sipped like a "beef tea." This material should be used together with full doses of iron, to which it acts as a supplement.

Liver exercises a dramatic curative effect in pellagra, provided the disease has not progressed to a hopeless degree. It is best given as whole liver by mouth—one-half pound daily. The exact effect of the various commercial liver extracts has not yet been determined.

Liver feeding, as well as injection of extract, has been useless in our hands in other diseases of blood such as leukemia, neutropenia, thrombopenia, and aplastic anemia.

Detailed specifications of the various liver preparations, which have been approved by the Council on Pharmacy and Therapy of the American Medical Association, are to be found in New and Non-Official Remedies. The physician is advised, as a rule, to make his selection from this list.

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OTHER GLANDULAR EXTRACTS: SUCH AS POSTERIOR PITUITARY HORMONES AND THE MALE SEX HORMONE

RALPH ARTHUR REYNOLDS, M. D. (490 Post Street, San Francisco).—Posterior lobe extracts may be distinguished from most of the hormones in that they have been used clinically and experimentally as drugs, in addition to being used as replacement therapy in glandular deficiencies. The posterior lobe of the pituitary gland is made up of two distinct types of tissue, "pars intermedia" and "pars nervosa." The pars intermedia is thin, is poorly vascularized and is formed of densely packed basophil cells. It is believed by most workers that this portion contains the active principles referred to as posterior lobe hormones. The pars nervosa consists mainly of neuroglial elements and is highly vascular. While extracts of pars nervosa may yield "pituirrin," it is hardly probable that an entirely non-glandular tissue such as this should manufacture a secretion. The pars nervosa is much more likely to be the vehicle for transmission of the secretion formed by the intermedia into its blood vessels, or into the cerebro-spinal fluid of the third ventricle.

The term "pituirrin" is used as a convenient way of referring to crude extracts of the posterior lobe. Fühner, in 1913, isolated a pure crystalline basic substance which was placed upon the market in the form of its sulphate, hypophysin. The two terms, "pituirrin" and "hypophysin" have been used interchangeably, but pituirrin is now the more accepted term. Crude extracts of the posterior lobe (pituirrin) contain:

1. *Vasopressin*, or *pitressin*, which is responsible for raising blood pressure and constricting capillaries;

2. *Oxytocin* or *pitocin*, which stimulates the uterus, but has a negligible effect on the blood pressure; and

3. *Antidiuretic hormone*. According to Kamm, the anti-diuretic action of pituitary extracts is due wholly to vasopressin, but many workers believe that the renal action may be due to yet a third principle.

4. *Histamin*. As is the case with all tissue extracts, crude posterior lobe extracts contain histamin, which can be removed by prolonged treatment with alcohol; but for purposes of this discussion, this product can be ignored.

Since the whole posterior lobe extract may be fractionated into two relatively pure preparations, one characterized by pressor activity and the other by oxytocic activity, it becomes a matter of interest to know which preparations are responsible for certain specific physiologic functions in the human body.

A. Antidiuresis.

It has long been known that pituitrin exercises an antidiuretic effect in diabetes insipidus, which disease is usually regarded as resulting from a derangement in function of the posterior lobe. Melville and Halman, in quite recent work at McGill University, have obtained results in polyuric dogs which indicate that the antidiuretic effect is due to the pressor principle. The oxytocic constituent exerts no antidiuretic action which could not be attributed to contamination with pressor substance.

These investigators have also pointed out that, under certain conditions, the vaso-pressin substance will produce diuresis. It seems probable, however, that pitressin diuresis is observed only with preparations and doses which affect the circulation. While the diuretic action of posterior lobe extracts is probably due to vascular changes produced in the kidney, experimental work suggests that the antidiuretic action is not due to these vascular changes; the pressor fraction probably stimulates the epithelium of the renal tubules to absorb more water and thus to concentrate the urine. Pitressin, therefore, is being used more extensively at the present time in cases where it is desired to prevent excessive loss of water from the body tissues. It may be found useful in certain cases of nocturnal enuresis, given either intranasally or by hypodermic injection.

B. Blood pressure.

Oliver and Schafer (1895) first reported that an extract of the pituitary gland raised the blood pressure. Soon afterward Howell determined that this effect was produced by extract from the posterior lobe alone. Injection of pituitrin will cause a contraction of arterioles, thereby producing a slow rise in blood pressure. There is usually a slowing of the heart rate, while the force of the heart

may be slightly increased. (There is little experimental evidence to suggest that pituitrin is of any value as a cardiac stimulant in man.) This effect on blood pressure in man is due to the pressor principle in pituitrin, and is produced by constricting the arterioles. A second injection will often produce a fall in blood pressure. Probably the body develops an immunity to vaso-pressin, but it is thought by most investigators that this depressor substance is histamin.

C. Uterine contractions.

The posterior lobe of the pituitary is possibly one of the factors concerned in the onset of parturition. The uterus is not normally contractile during the first half of pregnancy: the spontaneous activity of the organ rises during the second half of pregnancy, and reaches its climax with the onset of labor. The corpora lutea may be responsible for the early quiescent stage; if the corpora lutea are made to persist longer than usual by injection of anterior pituitary extracts, it is found that the period of gestation is correspondingly prolonged. Oestrin, on the other hand, slightly stimulates the uterus and markedly increases its responsiveness to the oxytocic fraction of the posterior lobe. Oxytocin, or pitocin, cannot produce abortion in pregnant women, except sometimes late in pregnancy when combined with other measures such as quinin injections and purgation. During labor, however, it powerfully increases the uterine contractions and helps to expel the foetus, and later the placenta. Due to the fact that pitocin contains the fraction from the posterior lobe that will produce strong uterine contractions (but does not, at the same time, affect the blood pressure), it is to be recommended over pituitrin. It is particularly useful in postpartum hemorrhage and in atonic uteri.

D. Other organs.

The smooth muscle of the bladder and of the small and large intestine are stimulated. It is probable that the pressor fraction is responsible for intestinal stimulation, although both the pressor and oxytocic constituents of the posterior lobe will produce defecation in the unanesthetized dog.

Black has recently reported a series of cases in which pitressin was used postoperatively in the prevention of distention. Pitressin has also been used successfully in combating the distention following peritonitis.

Postpituitary products stimulate smooth muscle widely throughout the body; this action is thought to be a direct one, and is independent of the integrity of the nerve supply of the tissues concerned.

E. Action on metabolism.

There are a certain number of observations which suggest that posterior lobe function is related to the processes of metabolism. It has not been definitely established that cases of adiposity resulting from pituitary damage are due to reduction of pituitary function or are due to accidental injury to adjacent structures such as the tuber cinereum. Furthermore, it is not known definitely

whether or not the adiposity is due to a change in the water balance, or entirely to a fat deposition. It is known that the administration of pituitrin will cause a rapid and spectacular decline in weight in certain types of so-called pituitary obesity cases. It is my opinion that these cases represent water-balance upsets rather than real fat deposition.

Pituitrin will usually produce a transient rise of blood sugar, and occasionally a glycosuria. This is thought to be due to its antagonistic action to insulin. Pituitrin may be employed successfully in cases of insulin shock. It will cause a rapid rise of blood sugar and relieve convulsions and other symptoms of hypoglycemia.

MALE SEX HORMONE

For purposes of this discussion it is hardly necessary to enumerate the work of such investigators as Voronoff, Steinach and Stanley, since their experimental work has not been so much concerned with isolation of the male sex hormone as it has been with transplantation and reactivation of the testes. The most positive investigations in the direction of isolating the male sex hormone are those of Koch, Funk, McCulloch, McGee and others. Specific reactions produced by extracts presumably containing the male sex hormone have been based on the growth of a cock's comb and the restoration to normal of atrophic and functionless secondary genital organs in castrated animals. Extracts of bull's testicles that will prolong the life of spermatozoa in the epididymes of completely castrated guinea-pigs have been prepared. The male sex hormone has also been recovered in the urine of men, and a gonad-stimulating hormone has been recovered in the urine of pregnant and nonpregnant women.

Comparatively recent work has shown that injection of the male sex hormone in immature male rats produces a striking increase in the size of the seminal vesicles and the prostate gland. When combined with follutein, or with the urine of pregnancy, the change in these organs is still more striking. Thus far, the male sex hormone has not been definitely isolated and purified; but with constant improvement and extension of methods of assay for testicular hormone, it seems reasonable to assume that this important and elusive hormone will before long be isolated.

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THE POSSIBILITY OF HORMONE IMBALANCE AS A CAUSE OF ESSENTIAL HYPERTENSION

FRANKLIN R. NUZUM, M. D. (Santa Barbara Cottage Hospital, Santa Barbara).—Although the etiology of hypertension seems complex, definite advances have been made in our knowledge of this subject. Hypertension due to tumor of the adrenal glands is now definitely recognized. It may be paroxysmal in type and often reaches high levels. Hypertension that is associated with coarctation of the aorta is another distinct type. In

young individuals, particularly, this condition should be thought of. The increase in blood pressure that is associated with glomerular nephritis; that associated with the toxemia of pregnancy, and that frequently associated with obesity, may easily be classified.

There still remains that very large and important group generally known as "essential hypertension." The causes in this group are still problematical; and the theories offered in explanation are legion. One of the newer theories, and one which holds great interest because it seems logical, is that suggesting the possibility of a hormonal disturbance in this condition.

In 1903, Abelous and Bardier described a depressor substance in the human urine. Twenty years later Pribram and Herrnheiser demonstrated that this substance was nondialyzable. In 1928, Professor E. K. Frey, chief of the surgical clinic of the medical academy at Düsseldorf, and his associate, Heinrich Kraut, described in detail work with this substance. He found that at least 80 per cent of it was manufactured by the pancreas; that it was present in the blood stream in an inactive form, and that it was excreted in the urine in an active form. He called it a hormone (Kallikrein), and demonstrated that it was not elaborated by other endocrine glands. He and Dr. Albert H. Elliot have demonstrated that it neutralizes the effect of adrenalin; that it causes a drop in blood pressure, when injected into an experimental animal, and that, at the same time, it increases the amplitude of the heart beat.

Adrenalin is the most active pressor substance known. Professor Frey postulated that hypertension might result from a lessened amount of Kallikrein in the circulating blood stream and, therefore, a loss of balance between this substance (Kallikrein) and adrenalin. Theoretically, this is a most interesting explanation of essential hypertension.

My associate, Doctor Elliot, and I have demonstrated that the urines of persons with essential hypertension contain less amounts of Kallikrein than the urines of normal persons in the same age groups. It was found necessary to divide normal individuals into three groups: those between 20 and 40 years of age averaging, in a twelve-hour night sample of urine, a Kallikrein output of approximately 3,800 units; those between 40 and 60 years averaging 2,700 units; and those from 60 years on, averaging 1,700 units. In an equal number of individuals with essential hypertension, those between 20 and 40 years averaged 2,500 units; between 40 and 60 years, 1,600 units; and from 60 years on, 650 units.

It is, therefore, apparent that individuals with essential hypertension throw out in the urine very materially lessened amounts of this substance. A further step in proving or disproving this hypothesis, as to the cause of hypertension, would be the giving to patients who secrete a lowered amount of this material in the urine regular doses of Kallikrein, intramuscularly. We are following this procedure with a small group of individuals. We

are not yet prepared to state what the outcome will be. Kallikrein may be obtained in this country from the Winthrop Chemical Company, under the trade name, Padutin. It should be given hypodermically, 1.0 cubic centimeter per dose, and from three to five times per week. No untoward side-reactions have resulted following this plan.

ASSEMBLY BILL

No. 2397

INTRODUCED BY MR. HEISINGER

March 27, 1935

Referred to Committee on County Government

An act to add section 4041.16 to the Political Code, relating to the powers of the boards of supervisors.

The people of the State of California do enact as follows:

- 1 SECTION 1. Section 4041.16 is hereby added to the
- 2 Political Code to read as follows:
- 3 4041.16. Under such limitations and restrictions as
- 4 are prescribed by law, and in addition to jurisdiction
- 5 and powers otherwise conferred, the boards of super-
- 6 visors, in their respective counties, shall have the juris-
- 7 diction and powers to provide systems of hospital in-
- 8 surance available to the residents of their respective
- 9 counties, and the board of supervisors of any county
- 10 shall establish such a system upon the petition of
- 11 twenty-five per cent of the registered voters of the
- 12 county. Any system of hospital insurance established
- 13 under this section shall provide for voluntary subscrip-
- 14 tions thereto by those residents desiring to benefit
- 15 therefrom. The supervisors shall establish subscrip-
- 16 tion rates to be paid monthly or otherwise by the sub-
- 17 scribers and shall prescribe the kind and extent of
- 18 hospital services available upon paying the established
- 19 rates therefor; and may provide for payments by sub-
- 20 scribers over the minimum rates established for mini-
- 21 mum services to entitle them to further or more special
- 22 services, such as private or semiprivate rooms, drugs,
- 23 additional or special nursing services, or such other
- 24 things as the particular board of supervisors may find
- 25 it expedient to furnish in return for such additional
- 26 payments.
- 27 In any such system every subscriber thereto shall be
- 28 entitled to the choice of his own doctor or physician
- 29 and shall pay such doctor's or physician's fees for
- 30 services rendered; but, in the cases of childbirth or of
- 31 indigency of the subscriber, the board of supervisors
- 32 shall provide medical care and treatment at county
- 33 expense. Every board of supervisors establishing such
- 34 a system shall prescribe rules and regulations for the
- 35 conduct and administration thereof, including the ter-
- 36 mination of subscribers' rights for nonpayment of
- 37 monthly or other subscriptions and the reinstatement
- 38 of rights upon payment of delinquencies.
- 39 In any county where such system is established, the
- 40 board of supervisors shall have power to rent or lease
- 41 established hospitals or wings or portions thereof, and
- 42 the total annual rental paid therefor by the county
- 43 shall not exceed a sum equal to six per cent per annum
- 44 of the actual appraisal of the property so rented
- 45 or leased. Should two or more contiguous counties
- 46 establish such systems of health insurance, such
- 47 counties may jointly rent or lease hospital facilities
- 48 for the convenience of their respective subscribers.
- 49 Should the funds received from payments by the
- 50 subscribers under such system be insufficient to en-
- 51 tirely defray the expenses in connection therewith,
- 52 the board of supervisors may levy an additional tax
- 53 upon all the property in the county, not to exceed
- 54 per cent per annum, to help support the sys-
- 55 tem; but any system shall be abolished which is found
- 56 impractical because the total revenue from subscrip-
- 57 tions and taxation is insufficient for its support.
- 58 SEC. 2. This act shall be known and may be cited
- 59 and referred to as the Hospital Insurance Act of 1935.

The key to the world of the future and to the wise fraternity of all races lies in the liberation of the child from the bondage of others' error and sin; from disease and debility, from desertion and want, from ignorance and passion above all, that are visited on the helpless to the third and fourth generation. The heart of a child is friendly to all; like the baby of Della Robbia its limbs are bound, but its arms go out to its fellows. Its single claim is to be allowed to love; its one revenge to die if, for an hour, we neglect it.—Romain Rolland.